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Prolonged Anginal Perceptual Threshold in Diabetes: Effects on Exercise Capacity and Myocardial Ischemia

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Anginal perceptual threshold (the time from onset of 0.1 mV of ST segment depression to onset of angina during treadmill exercise) is prolonged in diabetic patients with coronary artery disease. In the present study, the functional significance of this perceptual abnormality was evaluated by analysis of its effect on exercise capacity and the severity of myocardial ischemia. Treadmill exercise in 32 diabetic patients and 36 nondiabetic control patients showed a close linear correlation between the time to onset of electrical ischemia (ST segment depression) and exercise capacity in both groups ($r = 0.8$ and 0.9, respectively; $p < 0.001$). However, the slope of the relation was flatter in the diabetic group because prolongation of the anginal perceptual threshold permitted continued exercise as ischemia intensified. The anginal perceptual threshold itself showed a close linear correlation with exercise capacity in the diabetic group ($r = 0.8$, $p < 0.001$), although in the nondiabetic group these variables were unrelated.

The permissive effect of a prolonged anginal perceptual threshold on exercise capacity is undesirable as reflected by its correlation with ischemia at peak exercise ($r = 0.6$, $p < 0.001$): the longer the threshold, the greater the exercise capacity and the more severe the ischemia. Indeed, the inverse relation between the severity of ischemia at peak exercise and exercise capacity in the nondiabetic group ($r = 0.4$, $p < 0.02$) was completely lost in the diabetic group.

Thus, in diabetic patients with coronary artery disease, anginal perceptual threshold is a major determinant of exercise capacity. Prolongation of this threshold deprives the patient of the signal to stop exercising as the heart becomes ischemic. The more prolonged the threshold, the longer exercise continues and the more severe ischemia becomes. The adverse effects of this process on arrhythmogenesis and ongoing myofibrillar damage remain to be determined.

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We (1) have previously shown that in diabetic patients with symptomatic coronary artery disease, the perception of angina after the onset of exercise-induced ST segment depression is significantly delayed compared with that in nondiabetic patients. Cardiovascular tests of autonomic function suggested that the prolonged anginal perceptual threshold in diabetic patients was partly the result of damage to the sensory innervation of the heart, representing a previously unrecognized feature of diabetic neuropathy. The functional and physiologic significance of this perceptual abnormality, however, remains undetermined and we have, therefore, extended our observations in the same group of patients to determine the effects of prolonged anginal perceptual threshold on exercise performance and electrocardiographic (ECG) indexes of myocardial ischemia.

Methods

Study patients. Patients were selected from the cardiac and diabetic clinics of Newham General Hospital and community-shared diabetic clinics that have been established in the Health District. All patients had typical exertional angina and, for inclusion in the study, were required to be in sinus rhythm with an abnormal treadmill stress test result limited by angina and associated with diagnostic ST segment changes. Patients were excluded if they had unstable angina, myocardial infarction within the previous 3 months or ECG abnormalities preventing adequate interpretation of the exercise stress test (left bundle branch block, paced rhythms or

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Table 1. Clinical Characteristics of 68 Patients

	Diabetic Patients (n = 32)	Nondiabetic Patients (n = 36)	p Value
Mean age ± SD (yr)	58 ± 10	62 ± 8	NS
Gender (M/F)	23/9	28/8	NS/NS
Current smokers	7	15	NS
Hypertension	11	8	NS
Duration of angina (yr)	3.4 ± 3.2	5.6 ± 5.5	NS
Antianginal drugs*			
0	7	4	NS
1	10	16	NS
2	13	15	NS
3	0	1	NS
Q waves on ECG			
Anterior	14	8	NS
Inferior	2	7	NS
Coronary arteriography			
One vessel disease	4	0	NS
Two vessel disease	4	5	NS
Three vessel disease	12	19	NS
Total no. of patients	20	24	NS

*Long-acting nitrates, beta-adrenergic blocking agents and calcium antagonists; 11 patients (7 diabetic, 4 nondiabetic) entered into the study at the time of diagnosis were receiving no treatment. ECG = electrocardiogram; F = female; M = male.

digoxin-induced ST segment or T wave changes). Also excluded were patients with diabetes who had proteinuria (Albustix positive) or symptomatic neuropathy or retinopathy severe enough to warrant treatment. Patients were not questioned about impotence.

Forty-two diabetic and 42 nondiabetic patients were originally selected for the investigation. Two patients with diabetes were excluded because of frequent ventricular ectopic activity. A further eight diabetic and six nondiabetic patients were excluded because they failed to develop chest pain during treadmill stress testing despite diagnostic ST segment depression in each case. The remaining 32 diabetic and 36 nondiabetic patients are the subjects of this study (Table 1). A total of 44 patients (20 with and 24 without diabetes) representing 65% of the group have now undergone cardiac catheterization, confirming coronary artery disease in every case. Of the 24 remaining patients, 13 had documented Q wave infarction, and the probability of coronary artery disease in the other 11 was very high in view of the typical history of angina, the age and gender distribution of the study group and the abnormal treadmill exercise test results (2). The 32 patients with diabetes were all under the care of a diabetic clinic and had been diagnosed on the basis of fasting hyperglycemia; 9 were treated with insulin and the remainder received oral hypoglycemic drugs. They had been diagnosed 8.5 ± 5.4 years previously and had glycosylated hemoglobin levels of 8.9 ± 0.4% (normal range <9.0%). All patients gave written informed consent for participation in this study, which had been approved by the Newham Health District Ethical Committee.

Treadmill stress testing. All antianginal drugs except sublingual nitroglycerin were stopped at least 12 h before treadmill stress and autonomic function testing. Symptom-limited exercise testing was performed on a motor-driven treadmill according to the Bruce protocol (3). Patients exercised in 3 min stages at progressively increasing work loads. A 12 lead ECG was recorded before exercise, at the end of each 3 min stage, at peak exercise and every minute during recovery. Heart rate and blood pressure were recorded at the same intervals. The three ECG leads previously identified as showing the earliest ST depression were recorded continuously throughout exercise on the ECG printout to identify the time to onset of 0.1 mV of ST depression measured 80 ms after the J point. The time to onset of angina was also recorded and the anginal perceptual threshold calculated as the difference between these times. Four patients (all in the nondiabetic group) in whom angina occurred before the onset of ST depression were assigned an anginal perceptual threshold of zero in acknowledgment of the fact that angina, by definition, cannot precede the development of myocardial ischemia.

Statistical analysis. All averaged results are expressed as mean values ± 1 SD. The significance of differences between the diabetic and nondiabetic groups was obtained by the Mann-Whitney *U* test. Determinants of exercise tolerance and myocardial ischemia at peak exercise were obtained by linear regression analysis.

Results

There were no important differences between the diabetic and nondiabetic groups in terms of age and gender distribution, antianginal medication and ECG signs of previous myocardial infarction (pathologic Q waves). Cardiac catheterization performed in 65% of the patients confirmed that the distribution of coronary artery disease in the two groups was similar (Table 1).

Hemodynamic and symptomatic responses to exercise (Table 2). Values for heart rate at rest were similar in the diabetic and nondiabetic groups, but blood pressure in the group with diabetes was higher. Exercise produced normal increases in heart rate and blood pressure and both groups achieved similar peak rate-pressure products, with ST segment depression and angina in every case. The onset of 0.1 mV of ST segment depression, however, occurred significantly earlier in the group with diabetes, but because the anginal perceptual threshold was an average of 86 s longer (95% confidence interval 53 to 119 s), the time to onset of chest pain was not significantly different from that of the group without diabetes.

Determinants of exercise capacity. In both groups, exercise capacity was similar and showed a close linear correla-

Table 2. Treadmill Stress Test Results

	Diabetic Patients (n = 32)	Nondiabetic Patients (n = 36)	p Value
Heart rate (beats/min)			
Rest	78 ± 13	75 ± 15	NS
Peak	125 ± 22	128 ± 20	NS
Systolic blood pressure (mm Hg)			
Rest	152 ± 25	138 ± 19	<0.05
Peak	164 ± 27	154 ± 26	NS
Peak rate-pressure product (mm Hg·beats/min × 10^{-3})	20.5 ± 5.3	19.7 ± 4.7	NS
Time to onset of 0.1 mV ST segment depression (s)	111 ± 82	216 ± 162	<0.005
Time to onset of chest pain (s)	261 ± 133	279 ± 159	NS
Anginal perceptual threshold (s)	149 ± 76	63 ± 59	<0.001
Sum of ST segment depression at peak exercise (mV)*	0.6 ± 0.3	0.7 ± 0.4	NS
Peak exercise time (s)	272 ± 136	309 ± 164	NS

*ST segment depression was summed in all leads showing ≥0.1 mV depression.

tion with the time to onset of 0.1 mV of ST depression; patients with earlier onset of ischemia had lower peak exercise times (Fig. 1A). In the diabetic group, however, the slope of the regression relation was appreciably reduced, reflecting the prolonged anginal perceptual threshold that permitted exercise to continue longer after the onset of myocardial ischemia. In this group, anginal perceptual threshold was itself a major determinant of exercise duration and the two variables showed a close linear correlation; in contrast, no relation could be demonstrated in the nondiabetic group (Fig. 1B).

Determinants of myocardial ischemia at peak exercise. The severity of myocardial ischemia at peak exercise (as judged by the sum of ST depression on the 12 lead ECG) was similar in the diabetic and nondiabetic groups. In the nondiabetic group, the severity of ischemia was inversely related to exercise duration, but in the diabetic group this relation was lost (Fig. 2A). The diabetic group, however, showed a highly significant correlation between the severity of ischemia at peak exercise and anginal perceptual threshold, patients with the longest threshold having the most severe ischemia. In contrast, there was no relation between these variables in the nondiabetic group (Fig. 2B).

Discussion

This study has shown that the prolonged anginal perceptual threshold in diabetes has important functional consequences, depriving the patient of the signal to stop exercising as regional ischemia intensifies. The more prolonged the anginal perceptual threshold, the longer the patient exercises and the more profound ischemia becomes, with complete loss of the normal inverse relation between exercise capacity and the severity of myocardial ischemia seen in nondiabetic patients.

Anginal perceptual threshold and exercise tolerance. In patients with coronary artery disease, the development of myocardial ischemia during exertion usually leads to angina, causing the patient to rest. Indeed, the time to onset of

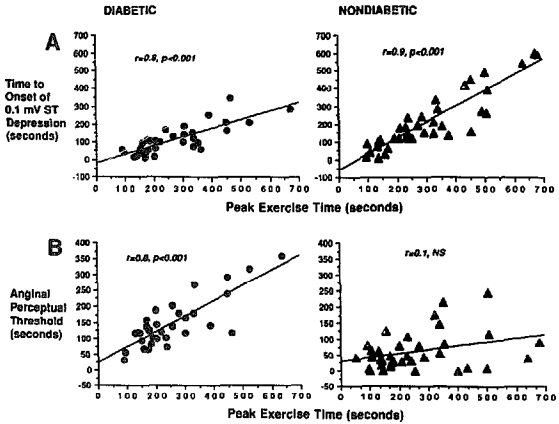

Figure 1. Relations between exercise tolerance and time to onset of myocardial ischemia (ST segment depression) (A) and anginal perceptual threshold (B), respectively, in 32 diabetic (circles) and 36 nondiabetic (triangles) patients.

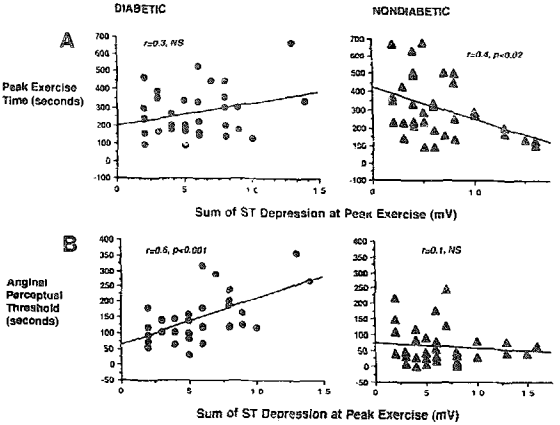

Figure 2. Relations between the severity of myocardial ischemia at peak exercise and exercise tolerance (**A**) and anginal perceptual threshold (**B**), respectively, in diabetic (**circles**) and nondiabetic (**triangles**) patients.

myocardial ischemia on ECG reflects the severity of coronary artery disease and is the major determinant of exercise capacity in these patients (4). Thus, in the present study, regression analysis showed a close correlation between the time to onset of exertional myocardial ischemia (as reflected by ST segment depression) and exercise tolerance in both the diabetic and the nondiabetic groups. In the diabetic group, however, the slope of the relation was considerably flatter, reflecting the prolonged anginal perceptual threshold that delayed the onset of symptoms and allowed exercise to continue before angina became limiting. Anginal perceptual threshold was itself an important determinant of exercise tolerance in the diabetic group and the more prolonged the threshold, the longer the patients were able to exercise.

Anginal perceptual threshold and exertional myocardial ischemia. Although prolongation of anginal perceptual threshold in the diabetic group was associated with increased exercise tolerance, our data indicate that this was undesirable because it allowed ischemia to intensify. In the nondiabetic patients, who had a relatively short anginal perceptual threshold, there was an inverse relation between exercise duration and myocardial ischemia: the more severe the ischemia, the sooner the patient stopped exercising. This relation was completely lost in the diabetic patients who showed a highly significant correlation between the severity of myocardial ischemia at peak exercise and anginal perceptual threshold, worsening perception of angina leading to increased exercise capacity and the development of more profound ischemia. The observation that the maximal ST depression was not greater in the diabetic group compared with the nondiabetic group may reflect the fact that total ST depression, though usually used to quantify ischemia, is not strongly predictive of the number of diseased vessels.

Clinical implications. The delay in the perception of angina after the onset of exertional myocardial ischemia deprives the diabetic patient of the signal to stop exercising and allows ischemia to intensify. Other investigators (5) have suggested that a defective anginal pain warning system in nondiabetic patients with silent myocardial ischemia is potentially hazardous and, by analogy, the same is likely to be true of diabetic patients with prolongation of anginal perceptual threshold. This perceptual impairment inevitably exposes the patient to an exaggerated ischemic burden with the attendant risks of arrhythmogenesis and myofibrillar damage. A high incidence of sudden death has been reported (6, 7) in diabetic patients with autonomic neuropathy and a prolonged anginal perceptual threshold may play an important role by exacerbating exertional ischemia and predisposing to lethal cardiac arrhythmias. Other factors, however, have also been suggested including extensive coronary artery disease (8,9) and QT interval prolongation (10).

The propensity of patients with diabetes to develop left ventricular failure, independent of the extent of coronary artery disease, is well documented (11–13) and various mechanisms have been proposed (14,15). Microvascular disease has been demonstrated histologically in patients with diabetic cardiomyopathy, and in the present study this might have accounted for the earlier onset of ST depression in the diabetic group compared with the nondiabetic group because the severity of epicardial coronary disease in the two groups

was similar (16). However, a prolonged anginal perceptual threshold may also contribute to the process of myofibrillar damage by exposing the patient to frequent and relatively prolonged periods of myocardial ischemia. It has been suggested that repetitive ischemic episodes of this type are important in the pathogenesis of ischemic cardiomyopathy and this appears particularly relevant in patients with diabetes, in whom progressive left ventricular dysfunction is common (17,18).

Conclusions. In patients with diabetes, prolongation of the anginal perceptual threshold has important functional consequences as emphasized by the effect it has on exercise performance. This study identified the anginal perceptual threshold as a major determinant of exercise capacity in patients with diabetes. With the development of exertional myocardial ischemia, the signal to stop exercising is delayed, permitting the patient to continue exercising as ischemia intensifies. Whether this predisposes diabetic patients to arrhythmic complications and ongoing ischemic injury is at present speculative and further studies are needed to answer these questions.

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